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\*Admitted only in Maryland  
\*Admitted only in Virginia  
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Federal Agencies

January 15, 2004

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Commissioner for Patents  
PO Box 1450  
Alexandria, VA 22313-1450

**Art Unit 1645**

Re: U.S. Utility Patent Application  
Application No. 10/668,326; Filed: September 24, 2003  
For: **N-Substituted Hydromorphones and the Use Thereof**  
Inventor: Donald J. Kyle  
Our Ref: 1861.1640001/JMC/THN

Sir:

Transmitted herewith for appropriate action are the following documents:

1. Information Disclosure Statement;
2. Form PTO-1449 (7 pages) citing twenty-one (21) references;
3. Copies of the twenty-one (21) cited references as listed on Form PTO-1449 (AR1-AT1; AR2-AT2; AR3-AT3; AR4-AT4; AR5-AT5; AR6-AT6; and AR7-AT7); and
4. Return postcard.

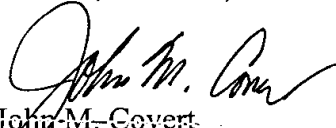
It is respectfully requested that the attached postcard be stamped with the date of filing of these documents, and that it be returned to our courier. In the event that extensions of time are necessary to prevent abandonment of this patent application, then such extensions of time are hereby petitioned.

Commissioner for Patents  
January 15, 2004  
Page 2

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

  
John M. Covert  
Attorney for Applicant  
Registration No. 38,759

JMC/THN/KPQ/dms  
Enclosures

218692-1



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

re application of:

Donald J. Kyle

Appl. No.: 10/668,326

Filed: September 24, 2003

For: **N-Substituted Hydromorphones  
and the Use Thereof**

Confirmation No: 2306

Art Unit: 1645

Examiner: *To Be Assigned*

Atty. Docket: 1861.1640001/JMC/THN

**Information Disclosure Statement**

Commissioner for Patents  
PO Box 1450  
Alexandria, VA 22313-1450

Sir:

Listed on accompanying Form PTO-1449 are documents that may be considered material to the examination of this application, in compliance with the duty of disclosure requirements of 37 C.F.R. §§ 1.56, 1.97 and 1.98. Copies of documents AR1-AT7 are also provided.

Copies of documents AA1 to AD2 are not provided in accordance with the U.S. Patent and Trademark Office pre-OG notice of July 11, 2003, which states "[t]he Office hereby waives the requirement under 37 CFR 1.98 (a)(2)(i) for submitting a copy of each cited U.S. patent and each U.S. patent application publication for all U.S. national patent applications filed after June 30, 2003."

Where the publication date of a listed document does not provide a month of publication, the year of publication of the listed document is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the month of publication is not in issue. Applicant has listed publication dates on the attached PTO-1449 based on information presently available to the undersigned. However, the listed publication dates should not be construed as an admission that the information was actually published on the date indicated.

Applicant reserves the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may

not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered.

This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist. The Examiner is specifically requested not to rely solely on the material submitted herewith.


This Information Disclosure Statement is being filed before the mailing date of a first Office Action on the merits. No statement or fee is required.

~~It is respectfully requested that the Examiner initial and return a copy of the enclosed PTO-1449, and indicate in the official file wrapper of this patent application that the documents have been considered.~~

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

  
John M. Covert  
Attorney for Applicant  
Registration No. 38,759

Date: Jan 15, 2004

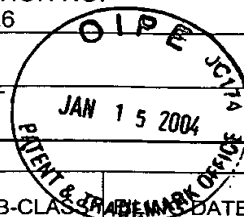
1100 New York Avenue, N.W.  
Washington, D.C. 20005-3934  
(202) 371-2600

FORM PTO-1449

## INFORMATION DISCLOSURE STATEMENT

ATTY. DOCKET NO.  
1861.1640001/JMC/THN  
FIRST NAMED INVENTOR  
Donald J. Kyle  
FILING DATE  
September 24, 2003

APPLICATION NO.  
10/668,326  
ART UNIT  
1645



## U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB-CLASS	REMARKS	DATE
	AA1	3,536,809	10/27/1970	Applezweig				02/17/1969
	AB1	3,598,123	08/10/1971	Zaffaroni				04/01/1969
	AC1	3,845,770	11/05/1974	Theeuwes <i>et al.</i>				06/05/1972
	AD1	3,916,899	11/04/1975	Theeuwes <i>et al.</i>				02/07/1974
	AE1	4,008,719	02/22/1977	Theeuwes <i>et al.</i>				02/02/1976
	AF1	5,059,595	10/22/1991	Le Grazie				03/20/1990
	AG1	5,073,543	12/17/1991	Marshall <i>et al.</i>				07/21/1988
	AH1	5,120,548	06/09/1992	McClelland <i>et al.</i>				11/07/1989
	AI1	5,354,556	10/11/1994	Sparks <i>et al.</i>				07/09/1990
	AJ1	5,591,767	01/07/1997	Mohr <i>et al.</i>				06/06/1995
	AK1	5,639,476	06/17/1997	Oshlack <i>et al.</i>				06/02/1995

## FOREIGN PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION
	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	1	Baumhaker, Y., and Sarne, Y., "Exposure of NG108-15 Cells to Etorphine Induces an Embedded State of the Opioid Receptor Which Discriminates Between Hydrophilic and Hydrophobic Ligands," <i>Pharmacology Communications</i> 7:149-155, Overseas Publishers Association and Harwood Academic Publishers (1996)
	AS	1	Brent, P.J., "Behavioural Effect of Pretreatment with Opioid Antagonists and Sigma Binding Site Ligands on the Abnormal Motor Response Produced by the Kappa Opioid Agonist U50,488H in Guinea Pigs," <i>Neuropharmacology</i> 32:751-760, Pergamon Press (1993)
	AT	1	Buchwald, H., <i>et al.</i> , "Long-term, continuous intravenous heparin administration by an implantable infusion pump in ambulatory patients with recurrent venous thrombosis," <i>Surgery</i> 88:507-516, The C.V. Mosby Company (1980)

EXAMINER

DATE CONSIDERED

**EXAMINER:** Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

FORM PTO-1449

## INFORMATION DISCLOSURE STATEMENT

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APPLICATION NO.

10/668,326

FIRST NAMED INVENTOR

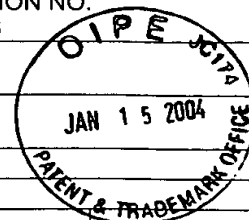
Donald J. Kyle

FILING DATE

September 24, 2003

ART UNIT

1645



## U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB-CLASS	FILING DATE
	AA2	5,674,533	10/07/1997	Santus <i>et al.</i>			05/26/1995
	AB2	5,698,155	12/16/1997	Grosswald <i>et al.</i>			01/24/1995
	AC2	5,733,566	03/31/1998	Lewis			10/30/1995
	AD2	6,294,195 B1	09/25/2001	Oshlack <i>et al.</i>			09/07/1999
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	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	2	During, M.J., <i>et al.</i> , "Controlled Release of Dopamine from a Polymeric Brain Implant: In Vivo Characterization," <i>Ann. Neurol.</i> 25:351-356, Little, Brown and Company (1989)
	AS	2	Foss, J.F., "A Review of the Potential Role of Methylnaltrexone in Opioid Bowel Dysfunction," <i>Am. J. Surg.</i> 182(Suppl. To November 2001):19S-26S, Excerpta Medica, Inc. (November 2001)
	AT	2	Goodson, J.M., "Dental Applications," in <i>Medical Applications of Controlled Release, Volume II Applications and Evaluation</i> , Langer, R.S., and Wise, D.L., ed., CRC Press, Inc., Boca Raton, FL, pp. 115-138 (1984)

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DATE CONSIDERED

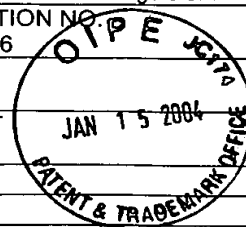
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	AN						Yes No
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## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

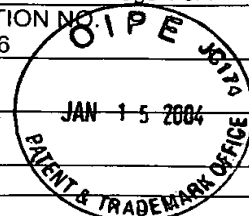
	AR	<u>3</u>	Griffiths, S.P., <i>et al.</i> , "Heterogeneous Enantioselective Hydrogenation Catalysed by Platinum Modified by Some Morphine Alkaloids," in <i>Catalysis of Organic Reactions</i> , Herkes, F.E., ed., Marcel Dekker, Inc., New York, NY, pp. 89-100 (1998)
	AS	<u>3</u>	Howard III, M.A., <i>et al.</i> , "Intracerebral drug delivery in rats with lesion-induced memory deficits," <i>J. Neurosurg.</i> 71:105-112, American Association of Neurological Surgeons (1989)
	AT	<u>3</u>	Hunskaar, S., <i>et al.</i> , "Formalin test in mice, a useful technique for evaluating mild analgesics," <i>J. Neurosci. Meth.</i> 14:69-76, Elsevier Science Publishers B.V. (1985)

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FORM PTO-1449  <b>INFORMATION DISCLOSURE STATEMENT</b>	ATTY. DOCKET NO. 1861.1640001/JMC/THN	APPLICATION NO. 10/668,326
	FIRST NAMED INVENTOR Donald J. Kyle	
	FILING DATE September 24, 2003	ART UNIT 1645

**U.S. PATENT DOCUMENTS**

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	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

**OTHER (Including Author, Title, Date, Pertinent Pages, etc.)**

	AR	<u>4</u>	Iorio, M.A., and Frigeni, V., "Narcotic agonist/antagonist properties of quaternary diastereoisomers derived from oxymorphone and naloxone," <i>Eur. J. Med. Chem. -Chim. Ther.</i> 19:301-303, Editions Scientifiques Elsevier (1984)
	AS	<u>4</u>	Langer, R., "New Methods of Drug Delivery," <i>Science</i> 249:1527-1533, American Association for the Advancement of Science (1990)
	AT	<u>4</u>	Langer, R., and Peppas, N., "Chemical and Physical Structure of Polymers as Carriers for Controlled Release of Bioactive Agents: A Review," <i>J. Macromol. Sci. Rev. Macromol. Chem. Phys.</i> C23:61-126, Marcel Dekker, Inc. (1983)

EXAMINER	DATE CONSIDERED
<b>EXAMINER:</b> Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.	

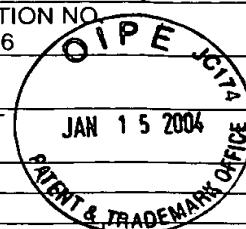


FORM PTO-1449

INFORMATION DISCLOSURE STATEMENT

ATTY. DOCKET NO.  
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Donald J. Kyle  
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APPLICATION NO.  
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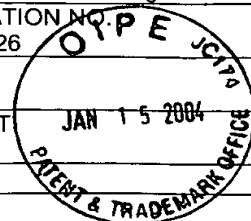
	AR	<u>5</u>	Leander, J.D., "A Kappa Opioid Effect: Increased Urination in the Rat," <i>J. Pharmacol. Exp. Ther.</i> 224:89-94, The American Society for Pharmacology and Experimental Therapeutics (1983)
	AS	<u>5</u>	Levy, R.J., <i>et al.</i> , "Inhibition of Calcification of Bioprosthetic Heart Valves by Local Controlled-Release Diphosphonate," <i>Science</i> 228:190-192, American Association for the Advancement of Science (1985)
	AT	<u>5</u>	Milne, R.J., <i>et al.</i> , "Quaternary naloxone blocks morphine analgesia in spinal but not intact rats," <i>Neurosci. Lett.</i> 114:259-264, Elsevier Scientific Publishers Ireland Ltd. (1990)

EXAMINER

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	FIRST NAMED INVENTOR Donald J. Kyle	
	FILING DATE September 24, 2003	ART UNIT 1645



## U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB-CLASS	FILING DATE
	AA6						
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## FOREIGN PATENT DOCUMENTS

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	AL6						Yes No
	AM6						Yes No
	AN6						Yes No
	AO6						Yes No
	AP6						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

AR	6	Murphy, D.B., <i>et al.</i> , "Pharmacokinetic profile of epidurally administered methylnaltrexone, a novel peripheral opioid antagonist in a rabbit model," <i>Br. J. Anaesth.</i> 86:120-122, Oxford University Press (January 2001)
AS	6	Panerai, A.E., <i>et al.</i> , "Opiates Act Centrally on GH and PRL Release," <i>Endocrinology</i> 108:2400-2402, The Endocrine Society (1981)
AT	6	Saudek, C.D., <i>et al.</i> , "A Preliminary Trial of the Programmable Implantable Medication System for Insulin Delivery," <i>N. Engl. J. Med.</i> 321:574-579, Massachusetts Medical Society (1989)

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DATE CONSIDERED

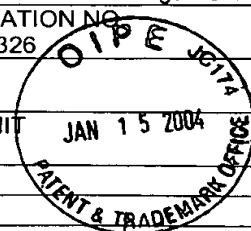
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**U.S. PATENT DOCUMENTS**

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB-CLASS	FILING DATE
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**FOREIGN PATENT DOCUMENTS**

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION
	AL7						Yes No
	AM7						Yes No
	AN7						Yes No
	AO7						Yes No
	AP7						Yes No

**OTHER (Including Author, Title, Date, Pertinent Pages, etc.)**

AR	<u>1</u>	Sefton, M.V., "Implantable Pumps," <i>Crit. Rev. Biomed. Eng.</i> 14:201-240, CRC Press (1987)
AS	<u>1</u>	Valle, L., <i>et al.</i> , "Effects of $\mu$ -opioid receptor agonists on intestinal secretion and permeability during acute intestinal inflammation in mice," <i>Eur. J. Pharmacol.</i> 389:235-242, Elsevier Science B.V. (2000)
AT	<u>1</u>	Yuan, C.-S., <i>et al.</i> , "Effects of Subcutaneous Methylnaltrexone on Morphine-Induced Peripherally Mediated Side Effects: A Double-Blind Randomized Placebo-Controlled Trial," <i>J. Pharmacol. Exp. Ther.</i> 300:118-123, The American Society for Pharmacology and Experimental Therapeutics (January 2002)

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